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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/754,922	01/09/2004	Jeffrey Stavenhagen	1301.0004C	8663

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EDELL, SHAPIRO & FINNAN, LLC
1901 RESEARCH BLVD.
SUITE 400
ROCKVILLE, MD 20850-3164

EXAMINER	
CROWDER, CHUN	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/754,922	STAVENHAGEN ET AL.	
	Examiner	Art Unit	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/13/06, 02/02/07, 04/11/007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92-132* is/are pending in the application.

4a) Of the above claim(s) *93-95,102-104 and 115-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92, 96-101, and 105-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/19/2006 and 12/07/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I drawn to a polypeptide comprising a variant Fc region and species of IgG1, 396L, FcγRIIIA, Her2/neu, and a composition without additional agent, filed 10/13/2006, is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicant's amendments to the claims, filed 02/02/2007, are acknowledged.

Claims 1-91 have been canceled.
Claims 92-132 have been added.

Claims 92-132 are pending.

Applicant's cancellation of claims 1-91 renders the Remark, filed 02/02/2007, moot.

3. In light of applicant's amendments, the following additional new Species Election has been set forth herein.

Species Election

4. This application contains claims directed to the following patentably distinct species of the claimed inventions:

Applicant is required to elect one particular polypeptide comprising a variant Fc region, wherein said variant Fc region differs from a wild-type Fc region by comprising at least an amino acid modification at position 396 and:

A) without further comprising additional amino acid modifications, **OR**
B) further comprising additional amino acid modifications.

If (B) is elected, applicant is further required to elect particular additional amino acid modifications at specific positions (e.g. 210M as recited in claims 94).

These species are distinct because polypeptides comprising variant Fc regions comprising amino acid modifications at different positions differ in structures, physicochemical properties and mode of action are different.

Applicant is required under 35 USC 121 to elect a single disclosed species of an antibody to which the claims would be restricted if no generic claim is finally held to be allowable.

5. Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

6. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

8. During a telephone conversation with applicant's representative Jeffrey Auerbach on 04/11/2007, a provisional election was made to prosecute the species of (A) encompassing a polypeptide comprising a variant Fc region comprising an amino acid modification at position 396 and without further comprising additional amino acid modifications.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Affirmation to this election must be made by applicant in responding to this Office Action.

Claims 93-95, 102-104, and 115-132 have been withdrawn from further consideration by the Examiner, under 37 C.F.R. 1.142(b), as being drawn to nonelected invention.

Claims 92, 96-101, and 105-114 are currently pending as they read on the elected invention of a polypeptide comprising a variant Fc region and species of IgG1, 396L without additional amino acid modifications, FcγRIIIA, Her2/neu, and a composition without additional agent.

9. The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

10. Applicant's IDSs, filed 04/19/2006 and 12/07/2006, are acknowledged and have been considered. The duplicative references have been crossed-out.

11. The application is required to be reviewed and all spelling, TRADEMARK, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent application, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 92, 96-101, and 105-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 92, 96-101, and 105-114 are indefinite in that they only describe the number of amino acid positions in the Fc region without reciting the numbering system.

It is suggested to amend the claim to recite the particular numbering system used (e.g. EU index as in Kabat).

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 92, 96-101, 105-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A) Claims 92, 96-101, 105-114 recite "a polypeptide comprising a variant Fc " as part of the invention, and claims 92, 96, 97, 99, and 100 recites "at least an amino acid modification" as part of the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The disclosure appears to show only antibodies with certain specified amino acid substitutions. For example, the specification discloses engineered antibodies such as anti-HER-2/neu antibody with amino acid substitutions in the Fc region (e.g. see Table 4 on pages 62-63 and Table 6 on pages 119-123 of the specification as-filed). The instant claims encompass in their breadth *any* "a polypeptide comprising a variant Fc " comprising with at least one amino acid substitutions.

However, there does not appear to be sufficient guidance in the specification as field as to how the skilled artisan would make and use the claimed "a polypeptide comprising a variant Fc " comprising with at least one amino acid substitutions. The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies.

For example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969. Reference C78 on IDS) show that even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968). Further, Lazar et al. (WO 03/074679, reference B22 on IDS) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an antibody to be more soluble may cause a loss in affinity for its antigen (see entire document, particularly page 3).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict such "a polypeptide comprising a variant Fc " comprising with at least one amino acid substitutions to have the same function as the instant claimed invention.

Reasonable correlation must exist between the scope of the claims and scope to enablement set forth. Applicant does not appear to provide guidance as to other "a polypeptide comprising a variant Fc " comprising with at least one amino acid substitutions which meets the claimed limitation of increased affinity to an FcγR.

In addition, the specification does not appear to provide sufficient guidance as to which residues should or should not be changed to preserve any particular function. Although the specification does provide working examples of antibodies such as antibodies with specific position(s) in the Fc region altered (e.g. see Table 10 on page 182-185); however, certain amino acid modifications in the Fc region do not increase affinity to FcγR (e.g. see clone 8, 16-19 in Table 10 on pages 182-185). Yet the variations permitted by the instant claim language is extensive.

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed "a polypeptide comprising a variant Fc " comprising with at least one amino acid substitutions. The specification provides insufficient direction or guidance regarding how to produce "a polypeptide comprising a variant Fc " comprising with at least one amino acid substitutions as broadly defined by the claims.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant is invited to consider amending the claimed polypeptide to antibody to obviate this rejection.

B) Claim 114 recites "pharmaceutical composition" as part of the invention.

Although the claim is read in the context of the elected species of antibody that binds Her2/neu cancer antigen, the following is noted:

The specification does not adequately teach how to effectively use a "pharmaceutical composition" comprising any antibody that binds any cancer antigen or antigen associated with an infectious disease to treat any disease or reach an appropriate beneficial therapeutic endpoint. The specification does not appear to provide working examples showing that "pharmaceutical composition" comprising any antibody that binds any cancer antigen or antigen associated with an infectious disease to treat any disease, nor does the instant specification disclose clinical experience with the claimed antibodies to the development of effective "pharmaceutical composition" to treat diseases broadly encompassed by the claimed invention and consistent with the disclosure of various diseases and disorders disclosed on pages 5-10 of the instant specification.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Vietta et al. (Science 2006 313:308-309) teach given the complex structure of antibodies, designing therapeutic antibodies can be unpredictable; in the case of anti-CD28 antibody, although preclinical data show that the antibody was safe when administered to two species of monkeys, healthy humans injected with the anti-CD28 antibody suffered immediate and profound side effects (see pages 308-309).

Therefore, in view of the quantity of experimentation necessary, the limited working example, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Amending the claim to delete "pharmaceutical" would obviate this rejection.

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 92, 96-101, and 105-114 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over:

claims 1-8, 10-30, 32, 42, 55, and 57-62 of the copending USSN 11/271,140,
claims 1-13, 18-22, 29-34, 42, and 43 of the copending USSN 11/502,820.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant and the copending application claims are drawn to same or nearly the same polypeptide variants comprising a variant Fc region wherein said variant Fc region differs from a wild-type Fc region by comprising at least an amino acid modification. Given the instant claims 92, 96-101, and 105-114 recite a species of polypeptide variants comprising Fc variants with at least one amino acid modification at position 396, in turn, the genus of polypeptide comprising a variant Fc region recited in copending claims would thus be anticipated by the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 92, 96-101, and 105-114 are directed to an invention not patentably distinct from claims 1-8, 10-30, 32, 42, 55, and 57-62 of the commonly assigned copending USSN 11/271,140 and claims 1-13, 18-22, 29-34, 42, and 43 of the commonly assigned copending USSN 11/502,820 for reasons stated above in Section 17.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned USSN 11/271,140 and 11/502,820, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chun Crowder, Ph.D.
Patent Examiner
April 12, 2007

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TC1600
4/11/07